Attorney Docket No. DSI-10402/22

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF APPEALS AND INTERFERENCES

In re Patent Application of:
Lawrence W. Cosenza

Application No.: 10/735,203 — Confirmation No.: 2593

Filed: December 12, 2003 — Art Unit: 1633

For: SACROMASTIGOPHORIC THERAPEUTIC AGENT DELIVERY SYSTEM — Examiner: Anne Marie Sabrina Wehbé

APPELLANTS' APPEAL BRIEF UNDER 37 CFR §41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on February 25, 2008, accounting for the requested extension of time, and is in furtherance of said Notice of Appeal.
The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.
This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

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I. Real Party in Interest

The real party in interest in this appeal is the assignee Diversified Scientific, Inc.

II. Related Appeals and Interferences

Appellant is aware of no appeals or interferences pending or otherwise related to the present appeal.

III. Status of the Claims

The present application was initially filed with 42 claims. Claims 3, 5-6, 9-10, 12-40, and 42 have been canceled. Claims 1, 2, 4, 7, 8, 11, and 41 are pending, finally rejected, and under appeal. Claims 1, 11, and 41 are the only pending independent claims.

IV. Status of Amendments Filed Subsequent Final Rejection

Claims 1, 2, 7, 11, and 41 were amended subsequent to final rejection. Claims 6, 9, and 13 were canceled subsequent to final rejection. All amended and canceled claims were entered and are reflected in the listing of claims on appeal in Appendix A.

V. Summary of the Claimed Subject Matter

Independent claim 1 relates to a therapeutic delivery system for a host wherein the delivery system has a therapeutic agent (page 7, lines 17-19), a sacromastigophoric organism (page 13, line 13) containing the therapeutic agent through packaging and a gene encoding full length primate Hpr (page 14, lines 1-5) wherein the gene has an inducible promoter (page 14, lines 1-2) and encoding a lysosomal targeting sequence (page 34, lines 3-4). Claim 2 relates to the system of claim 1 wherein a therapeutic agent is selected from the Markush group including drugs and prodrugs (page 5, lines 19-20). Claim 4 relates to the system of claim 1 wherein the

organism is selected from the Markush group including Trypanosoma, Plasmodium, Amoeba, Giardia, Entamoeba, and Leishmania (page 12, lines 19-23). Claim 7 relates to the system of claim 1 wherein the gene encoding full length primate Hpr is upregulated by a promoter responsive to an induction species exogenous to both the organism and the host. (page 5, lines 12-14). Claim 8 relates to the system of claim 7 where the induction species is an antibiotic. (page 14, lines 3-5).

Independent claim 11 relates to a therapeutic delivery system for a host that includes a trypanosome organism containing a gene encoding full length primate Hpr (page 14, lines 1-5) upregulated by a promoter responsive to an induction species exogenous to both the organism and the host (page 5, lines 12-14) and wherein the gene also has a lysosomal targeting sequence (page 34, lines 3-4).

Independent claim 41 relates to a sacromastigophoric organism for delivery of a therapeutic agent that is obtained by a process involving culturing sacromastigophoric organisms (page 5, line 22) that have been transfected with an expression vector (page 5, line 23) containing an expression cassette induced by a first exogenous species (page 5, line 23), wherein the cassette has a first construct having a first inducible promoter controlling expression of a gene encoding primate Hpr protein (page 18, lines 16-21) also present in said construct; said protein further comprising a lysosomal targeting sequence (page 34, lines 3-4).

VI. Grounds of Objection/Rejection to Be Reviewed on Appeal

A. Claims 1-2, 4, 7-8, 11 and 41 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement as is detailed in Paper No. 20061202.

B. Claims 1-2, 4, 7-8, 11 and 41 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement as is detailed in Paper No. 20061202.

C. Claims 11 and 41 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention as is detailed in Paper No. 20070812.

VII. Argument

The Examiner's Position

Examiner based his rejection of claims 1-2, 4, 7-8, 11 and 41 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement on the assertion that "The specification lacks sufficient written description for 1) recombinant Hpr or nucleic acids encoding Hpr other than human Hpr." (Paper No. 20061202, page 5, second paragraph.) Expanding, the rejection states: "The specification does not provide sufficient written description for the genus of Hpr proteins or nucleic acids encoding Hpr proteins other than human Hpr protein and a cDNA encoding human Hpr." Id. In support of an assertion that Hpr is only present in apes, old world monkeys, and chimpanzees, Examiner cites Smith et al. (1995) *Science*, Vol. 268,284-286, see pages 285-286, bridging paragraph. As such, Examiner concludes that the specification lacks written description for recombinant Hpr or nucleic acids encoding Hpr other than human Hpr.

Examiner based his rejection of claims 1-2, 4, 7-8, 11 and 41 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement based on the assertion that "[t]he specification does not provide an enabling disclosure for making any Trypanosome which

contains a recombinant Hpr protein or a nucleic acid encoding a Hpr, or which additionally contains a drug or prodrug." (Paper No. 20061202, page 8, second paragraph.) This assertion is based on a finding that:

> [T]he prior art teaches that contacting Trypanosomes with Hpr results in endocytosis of the protein and trafficking to lysosomes, where at least in the case of *Trypanosoma brucei brucei*, the presence of the Hpr protein in the lysosome results in lysis of the organism. However, for other species of Trypanosome, such as *Trypanosoma brucei rhodensiense*, Hpr does not have lytic activity, and Shimamura et al. hypothesize that this failure to lyse is the result of reduced endocytosis and failure to enter the lysosome (Shimamura et al. (2001) *Mol. Biochem. Parasitol.*, Vol. 115,227-237). (Paper No. 20061202, paragraph bridging pages 8-9.)

Thus, Examiner concludes that:

> [T]he presence of Hpr in *Trypanosoma brucei brucei* results in lysis of the organism such that the skilled artisan would not predict that *Trypanosoma brucei brucei* containing recombinant Hpr protein could be stably produced. Further, the prior art teaches the unpredictability of producing other species of Trypanosomes containing recombinant Hpr as it appears the Hpr is not effectively endocytosed or trafficked in these Trypanosomes. (Paper No. 20061202, page 9.)

The rejection is summarized in Paper No. 20080220 at page 3 which states that: "The issue is whether Hpr, when present in the lysosome, can in fact lyse all species of Trypanosome."

For the same reasoning presented in the rejection under 35 U.S.C. §112, first paragraph, written description, the subject claims are rejected on lack of enablement grounds as "The specification further does not provide sufficient guidance for making and using Trypanosomes containing a gene or cDNA encoding any Hpr as a drug delivery system." (Paper No. 20061202, page 9.) Thus, Examiner's position is that it would have required undue experimentation to isolate and use any species of Hpr other than human.

The rejections are further based on the assertion that the specification is unclear whether

human Hpr will successfully lyse Trypanosome species other than *Trypanosoma brucei brucei*. (Paper No. 20061202, page 10.) This is primarily based the cited finding by Shimamura et al., for instance, [which] clearly teaches that *Trypanosoma brucei rhodensiense* is not lysed by Hpr or the TLF complex comprising Hpr (Shimamura et al. (2001) supra, page 227)." Id. Thus, examiner concludes that it would require undue experimentation to make and use any species of Trypanosome as a drug delivery system.

The rejection takes note of examples 5 and 6 in the subject specification for mediating gene transfer in human or mouse cells. The rejection is based on the statement that the examples do not provide sufficient guidance for "intracellular expression of Hpr protein from a recombinant expression construct contained within the Trypanosome, [because] the examples do not include any data from any actual experiments demonstrating infection of any type of host cell followed by lysis of the host cell mediated by Hpr." Id.

Additionally, the rejection is based on a finding by Examiner that "[i]n the absence of any such lysosomal targeting sequence, Hpr would be secreted by the cell such that lysis of the Trypanosome would not occur. Further, constitutive expression of lysosomal targeted Hpr would result in lysis of the Trypanosome such that a stable organism could not be made or used to deliver a drug." (Paper No. 20061202, page 12.) Thus, examiner concludes that a skilled artisan would not anticipate success in making the proposed Trypanosomes.

Finally, the rejection states that "the specification fails to provide an enabling disclosure for delivering any drug or prodrug to any host cell using the modified Trypanosomes as claimed." (Paper No. 20061202, page 12.) Much of this reasoning is based on the finding that the examples teach delivery of a provirus, which Examiner does not equate with a drug or prodrug. Further, "[n]either the specification nor the prior art teach that drugs, either packaged

in a liposome as described by any of the reference patents or not, can be stably maintained in a Trypanosome, or subsequently released to a host organism upon lysis of the Trypanosome." Id. Thus, the rejection concludes that it would require undue experimentation to make and use the Trypanosomes as claimed.

Examiner based his rejection of claims 11 and 41 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention as "[c]laim 41 recites the limitation "said primate Hpr protein" in line 8; however, there is insufficient antecedent basis for this limitation in the claim." (Paper No. 20070812, page 15.) Examiner states that: "Amendment of this to 'primate Hpr protein' would overcome this rejection." Id. Regarding claim 11, the rejection appears to be stated as:

> A 'recombinant lytic factor', as recited in claim 1, is a protein, not a gene encoding a recombinant lytic factor. As such, claim 7 is confusing as it is unclear how a recombinant protein can be 'upregulated' by a promoter since promoters drive expression of genes and thus can only upregulate the 'expression' of a protein. Id.

As claim 11 recites the same language as claim 7, claim 11 was included in the rejection.

Appellant's Position

A. Rejection of claims 1-2, 4, 7-8, 11 and 41 under 35 U.S.C. §112, first paragraph, written description.

Claims 1-2, 4, 7-8, 11, and 41 are based on sufficient written description in the instant specification such that a person having ordinary skill in the art recognizes that Appellant had possession of the invention as of the filing date. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the

art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. Additionally, originally claims constitute their own description. See In re Koller, 613 F.2d 819, 204 USPQ 702 (CCPA 1980).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it.")

A complete nucleic acid sequence for Hpr in recombinant form is presented in the instant application as Seq. ID No. 28. (p. 34, lines 16-17; Figures 10, 11.) Therefore, the instant application provides sufficient written description of recombinant Hpr.

Further, Applicant presents a complete nucleic acid sequence for human Hpr as Seq. ID No. 28. (p. 34, lines 16-17; Figure 11.) The gene encoding full length Hpr, or a truncation

thereof, is only found in the primates: humans, gorillas, baboons, mandrills, chimpanzees, and sooty mangabeys. Lugli, EB et al, *Molecular & Biochemical Parasitology*, (2004); 138:9–20. Of these, only humans, baboons, and chimpanzees possess full length Hpr. Id. Further, these Hpr genes possess high sequence homology. Id. Previously, Hpr was detected in genes resulting in termination of transcription in chimpanzees. Smith et al, *Science*, (1995); 268:284-286. More recent studies by Lugli contradict those results and identify full length Hpr in chimpanzees as well. Thus, the total number of species of full-length primate Hpr genes is three. As the court in Regents of the Univ. of Calif. v. Eli Lilly & Co. stated: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." 119 F.3d at 1569. This standard is precisely met by the instant specification. The description by nucleotide and amino acid sequence of the cDNA for Hpr recites "structural features common to the members of the genus" given the high homology between the Hpr genes in primates. Id. Further, the nucleotide and amino acid sequences described recite "features [that] constitute a substantial portion of the genus" of which there exist only three members. The court in Eli Lilly likened a similar satisfactory number of species to that which satisfies the enablement requirement. As such, description is readily met for a genus with a full one third of the total number of species expressly described, particularly given the high degree of sequence identity between members of the genus of primate Hpr genes.

The teaching of Lugli, while being an post-dated publication, that only a few closely related species to humans express full length Hpr is supported by the findings of Examiner that none of the submitted references "provides any evidence that genes encoding full length Hpr

were known or available in the prior art at the time of filing in primates other than humans." (Paper No. 20080220, paragraph bridging pages 2-3.) The absence of any scientist finding other species that express full length Hpr is itself indicative that the size of the genus of primate Hpr sequences is minute and is, thus, adequately described by the disclosure of the sequence encoding human Hpr. References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. *Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992). Thus, the Lugli reference, which is appended as Evidence under Appendix B, may be properly considered as demonstrating that a person having ordinary skill in the art recognized that the genus of full length primate Hpr genes was exceedingly small and is adequately described by submission of the human sequence. Moreover, the previously referenced Lugli et al. reference is bolstered by the submitted references of McEvoy et al., Erickson et al., Shuey et al., Heidenreich et al. and Martinez et al. In particular, McEvoy et al. seems to have been referred to by Lugli et al. on the very point that a full length Hpr is present in a very limited number of species.

Moreover, the recitation of the term Hpr is sufficient to describe the genus Hpr genes expressed in primates. This is similar to the generic term halogen found to be sufficient to describe the members of the chemical halogens. *Bigham v. Godtfredsen*, 857 F.2d 1415, 1417 (Fed. Cir. 1988) ("[t]he generic term halogen comprehends a limited number of species, and ordinarily constitutes a sufficient written description of the common halogen species.")

A written description need not, and should not, disclose all "art-recognized equivalents." *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1561 (Fed Cir. 1991). The above described nucleotide sequences that have been effective in therapeutic models are known and obvious to one having ordinary skill in the art. As such, the instant specification, through express definition and

illustration, and as judged by the knowledge of the common practitioner in the art, conveys more than adequate written description to illustrate that Applicant had possession of the invention as of the filing date.

Thus, a person having ordinary skill in the art recognizes that Appellant had possession of the sequence for primate Hpr at the time of filing the subject application.

B. The rejection of claims 1-2, 4, 7-8, 11 and 41 under 35 U.S.C. §112, first paragraph, enablement.

Claims 1-2, 4, 7-8, 11, and 41 are based on sufficient description in the subject specification such that a person having ordinary skill in the art can make and use the invention without undue experimentation.

Enablement under 35 U.S.C. §112, first paragraph, is satisfied if a person having ordinary skill in the art can make and use the invention without undue experimentation. "[I]t is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in In re Forman. 230 U.S.P.Q. 546, 547 (BPAI 1986) They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In Re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

However, to comply with 35 U.S.C. §112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) (an invention directed to a general system to improve the cleaning process for semiconductor wafers was enabled by a disclosure showing improvements in the overall system). Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Finally, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The specification teaches how a gene encoding Hpr is operative to lyse Trypanosomes as claimed in the subject invention. The instant specification teaches that a "gene is generally under the control of an appropriate promoter, which may be inducible, repressible, or constitutive." (p. 8, lines 14-16.) A non-limiting example of a promoter responsive to an induction species is taught by the instant specification. As depicted in Figure 1, a construct containing a gene encoding Hpr is under the control of a Tet inducible promoter (PARP*). The inventive organism

constitutively expresses TetR that represses expression of the Hpr gene. (p. 20, lines 6-7.) Introduction of the inducer tetracycline removes TetR from the promoter removing the repression and allowing selectively timed expression of the Hpr gene leading to lysis of the organism. (p. 20, lines 7-11.)

As demonstrated in Example 3 the recombinant Hpr gene also "contains a lysosome targeting sequence." (p. 34, line 4.) An example of a functional 43 amino acid targeting sequence is taught by Alexander et al, 2002 (incorporated by reference p. 34, line 7). As taught by the specification, Hpr functions to lyse the Trypanosome following localization to the lysosome. (p. 34, line 3.) (emphasis added) Therefore, the instant specification teaches the introduction of a gene encoding Hpr under the control of the inducible PARP* promoter that results in the production of a Hpr protein that is targeted to the lysosome yielding lysis of the host Trypanosome.

Thus, Wands factors (2) the amount of direction or guidance presented, and (3) the presence or absence of working examples, are fully satisfied as the specification provides multiple working examples of how a gene encoding full length primate Hpr is selectively expressed in time and location such that a person having ordinary skill in the art can predict that *Trypanosoma brucei brucei*, or other Trypanosomes containing recombinant Hpr protein could be stably produced.

Contrary to Examiner's concern regarding the prior art of Shimamura, the system of the claims as taught by the specification is independent of the ability of the Trypanosome to endocytose Hpr for lysis because the Hpr is produced within the Trypanosome itself. As such, the example of *Trypanosoma brucei rhodensiense*, which demonstrates poor endocytosis of serum Hpr (Shimamura et al, *Mol. Biocehm. Parasitol.*, 2001; 115:227-37, Hager, KM and

Hajduk, SL, *Nature*, 1997; 385:823–26), is readily lysed by Hpr because the endocytotic pathway is completely bypassed in the claimed invention. Thus, the specification teaches methods for circumventing the endocytic requirement of *rhodensiense* allowing Hpr to lyse this species of Trypanosome as well as *brucei*.

It is difficult to ascertain Examiner's understanding of Shimamura's teaching. Examiner reads Shimamura as teaching that "lysis of *Trypanosoma brucei rhodensiense* 'may' be due to reduced endocytosis and failure to enter the lysosome" (Paper No. 20080220, page 3.) finding this to be insufficient teaching. However, a complete and careful reading of Shimamura reveals that the teaching that Hpr is ineffectively lysed in *Trypanosoma brucei rhodensiense* comes from the 1997 Nature article by Hager, KM. Hager, KM and Hajduk, SL, Nature 1997; 385:823–26. Therein, Hager teaches unequivocally that:

> The human sleeping-sickness trypanosome, *Trypanosoma brucei rhodesiense* is resistant to TLF. Our studies reveal that resistant trypanosomes fail to endocytose TLF yet continue to bind TLF through cell-surface receptors. On the basis of these results, we conclude that one mechanism of resistance of human sleeping-sickness trypanosomes to human serum is decreased internalization of receptor-bound TLF. (Hager, KM, 1997, abstract.) (emphasis added)

As Hpr is the lytic component of TLF, Hager, and hence Shimamura, unequivocally teach that the reason *Trypanosoma brucei rhodesiense* is resistant to lysis by Hpr is due to failure of that species of Trypanosome to endocytose Hpr. As is taught by the instant specification, the endocytotic pathway is entirely circumvented by the instantly claimed invention. Thus, a person having ordinary skill in the art is provided with working examples, and is fully enabled to use internally expressed and lysosomally targeted Hpr to lyse Trypanosomes *brucei* and *rhodesiense* without undue experimentation.

Appellant incorporates by reference the remarks *supra* that the specification contains sufficient written description of the genus of full length Hpr genes and protein such that a person of ordinary skill in the art recognizes that Appellant had possession of the genus on the filing date. A person of ordinary skill in the art is similarly fully enabled to make and use full length Hpr from the three primate species that express it without undue experimentation based on the specification teaching a highly representative example of the exceedingly small genus of primate Hpr protein sequences, all of which possess a high degree of sequence similarity. Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Methods of sequencing genes was well known and well established in the art at the time of filing such that sequencing related genes was considered common place and a mere step in the pathway to more significant scientific advancements. This is particularly true given the high homology between primate Hpr proteins such that design of sequencing and isolation primers was nothing more than reading a short sequence of the human Hpr sequence. Thus, by fully enabling a person having ordinary skill in the art to make and use 1/3 of the entire genus of species whose characteristics are well characterized and highly similar, the specification enables a person having ordinary skill in the relevant art to make and use Trypanosomes containing a gene or cDNA encoding any primate Hpr without undue experimentation.

Moreover, the specification provides concrete and relevant examples such that a person having ordinary skill in the art can intracellularly express Hpr protein from a "recombinant

expression construct contained within the Trypanosome." (Paper 20061202, page 10.) The Federal Circuit has held in In re Wands that among the factors to be considered when determining whether a specification is enabling is "(3) the presence or absence of working examples." 858 F.2d 851, 737 (Fed. Cir. 1988). By way of specific examples, the specification teaches that Trypanosomes organisms naturally infect "myoblast, fibroblast, and macrophages through interaction with gp83-TSA." (p. 4, lines 1-2; Villalta et al. (2001) (incorporated by reference, p. 4, line 2.) Further, Example 5 provides detailed teaching of infection of human myocardial cells, and Example 6 provides detailed teaching of an *in vivo* mouse model whereby the period and method of tetracycline administration are both detailed. Moreover, the expression of the PARP* expression system is taught to be increased 10^3-10^4 –fold range (p. 20, lines 9-11; Wirtz et al., (1999) (incorporated by reference p. 20, line 11).

Examples 5 and 6 are prophetic in language style yet provide detailed teaching of how to make and use the instant invention. "Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications." MPEP 608.01(p). "[A] specification need not contain a working example . . . ." In re Borkowski, 422 F.2d 904, 908 (C.C.P.A. 1970). The court in Borkowski went on to hold that an application providing a sufficient "jumping off" point for which a practitioner may use the invention is sufficient to satisfy the enablement requirement. *Id.* Additionally, the court in In re Strahilevitz held that a prophetic example is sufficient to satisfy the enablement requirement. 668 F.2d 1229 (C.C.P.A 1982). The instant specification provides numerous details including particular cell types, and infected organisms, as well as methods of detecting positively infected cells by the use of GFP. (Example 5.) The instant specification provides examples similarly detailed to those in Borkowski and Strahilevitz, and thus, satisfies the enablement requirement.

The claims each posses the element that the full length primate Hpr is under the control of an inducible promoter. In the absence of an induction species such as an antibiotic, a person having ordinary skill in the art recognizes that the Hpr gene is not expressed to produce protein in the Trypanosome. Thus, Examiner's assertion that a stable organism could not be made or used to deliver a drug because constitutive expression of lysosomal targeted Hpr would result in lysis of the Trypanosome is incorrect. As per the claims, the Hpr is not constitutively expressed.

Finally, drugs and prodrugs are taught by the specification to encompass genes encoding nucleic molecules. Drugs are defined to include molecules that are used as a medicine to treat a disease, disease system, or undiagnosed pain. A person having ordinary skill in the art recognizes that packaging such molecules into Trypanosomes is taught by the instant specification *inter alia* Examples 1-3. Trypanosomes are "transfected with an expression cassette" encoding host genome integration genes and a gene encoding lysosome targeted Hpr. (p. 5, lines 1-24 to p. 6, lines 1-2.) Methods of cell transfection are well known in the art and do not require undue experimentation for an ordinary practitioner to practice in the instant invention. Thus, the delivery of drugs or prodrugs is taught by the specification by example.

In sum, the specification provides numerous concrete, working examples of how a person of skill in the art can make and use a Trypanosome with a inducible gene encoding full length Hpr possessing a lysosomal targeting sequence without undue experimentation. The specification presents significant guidance and direction and numerous working examples such that ordinary practitioners, all of who are highly skilled with experience and knowledge in the well understood fields of cell transfection, protein expression and protein targeting can make an use the invention without undue experimentation.

C. The rejection of claims 11 and 41 under 35 U.S.C. §112, second paragraph, indefiniteness.

Claims 11 and 41 were amended after final rejection, the contents of which were admitted and are captured in the listing of claims on appeal recited in Appendix A. The amendments are made in response to suggestions by the examiner and fully address the rejection. Regarding claim 11, the claim was amended identically to claim 7 for which the rejection was withdrawn in view of the amendment. Regarding claim 41, the word "said" was removed from the claim such that the phrase "primate Hpr protein" no longer lacks antecedent basis.

Appellant submits that withdrawal of claims 11 and 41 was not entered as a mere oversight and respectfully requests that the rejection of claims 11 and 41 be REVERSED in view of the previously entered amendments.

Conclusion

In summary, the specification fully describes the invention and enables a person having ordinary skill in the art to make and use the invention without undue experimentation by providing numerous working examples and a thorough description of all elements in the claims demonstrating that Appellant had full possession of the invention at the time of filing.

Accordingly, the rejection under 35 U.S.C. §112, first paragraph, written description with regard to claims 1-2, 4, 7-8, 11 and 41 should be REVERSED. Similarly, the rejection under 35 U.S.C. §112, first paragraph, enablement, with regard to claims 1-2, 4, 7-8, 11 and 41 should likewise be REVERSED. Finally, in view of the previously entered amendments the rejection under 35 U.S.C. §112, second paragraph, with regard to claims 11 and 41 should be REVERSED.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include all the amendments filed by Appellant.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 07-1180, under Order No. DSI-10402/22.

Date: May 27, 2008

Respectfully submitted,

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APPENDIX A

CLAIMS ON APPEAL

1. A therapeutic delivery system for a host comprising:

a therapeutic agent; and

a sacromastigophoric organism containing said therapeutic agent through packaging and a gene encoding full length primate Hpr; said gene further comprising an inducible promoter and encoding a lysosomal targeting sequence.

2. The system of claim 1 wherein said therapeutic agent is selected from the group consisting of: drugs and prodrugs.

3. (Canceled)

4. The system of claim 1 wherein the said organism is selected from the group consisting of Trypanosoma, Plasmodium, Amoeba, Giardia, Entamoeba, and Leishmania.

5-6 (Canceled)

7. The system of claim 1 wherein expression of said gene encoding full length primate Hpr is upregulated by said promoter responsive to an induction species exogenous to both said organism and said host.

8. The system of claim 7 wherein said induction species is an antibiotic.

9-10 (Canceled)

11. A therapeutic delivery system for a host comprising:

a trypanosome organism containing a gene encoding full length primate Hpr, expression of said gene is upregulated by a promoter responsive to an induction species exogenous to both said organism and said host; said gene further comprising a lysosomal targeting sequence.

12-40 (Canceled)

41. A sacromastigophoric organism for delivery of a therapeutic agent obtained by the process comprising:

culturing sacromastigophoric organisms that have been transfected with an expression vector containing an expression cassette induced by a first exogenous species, the cassette comprising:

a first construct having a first inducible promoter controlling expression of a gene encoding primate Hpr protein also present in said construct; said protein further comprising a lysosomal targeting sequence.

42. (Canceled)

APPENDIX B

EVIDENCE

Lugli, EB et al, *Molecular & Biochemical Parasitology*, (2004); 138:9–20.

APPENDIX C

RELATED PROCEEDINGS

There are no decisions that have been rendered by a court or the Board in any proceeding identified in the related appeal.